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Persistence of viral infections on the population level explained by an immunoepidemiological model

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Abstract

We consider a mathematical model of viral spread in a population based on an immune response model embedded in an epidemic network model. The immune response model includes virus load and effector and memory T cells with two possible outcomes depending on parameters: (a) virus clearance and establishment of immune memory and (b) establishment of a non-zero viral presence characterized with increased T-cell concentrations. Isolated individuals can have different immune system parameters and, after a primary infection, can either return to the infection-free state or develop persistent or chronic infection. When individuals are connected in the network, they can reinfect each other. We show that the virus can persist in the epidemic network for indefinite time even if the whole population consists of individuals that are able to clear the virus when isolated from the network. In this case a few individuals with a relatively weak immune response can maintain the infection in the whole population. These results are in contrast to implications of classical epidemiological models that a viral epidemic will end if there is no influx of new susceptibles and if individuals can become immune after infection.

Keywords: Viral infection; Immune response; Disease spread; Adenovirus

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1. Introduction

Clinical observations [1] show the following alternative outcomes from a non-lethal viral infection of an organism: (a) either the virus gets cleared and immune memory of the infection gets formed, or (b) a persistent infection characterized by a comparatively constant presence of virus in the organism gets established or (c) a chronic (latent) infection, characterized by fluctuating viral quantities. Which outcome occurs depends on the relation between the viral reproductive rate and the immune response of the individual organism. Depending on the individual host, the virus can reach in-host concentrations of various magnitudes. If the concentration is above some threshold, microparasite particles leave the host by various mechanisms and eventually colonize new hosts. The success of the transmission from one host to another depends on the quantity of emitted virus, on the distance between the hosts, on the immune status of the new host and other factors.

Classical epidemic models [2] incorporate these factors in the transmission and infectivity rates. These models do not differentiate between the individuals' immune responses and deal with classes of infectious, susceptible and recovered (immune) individuals where all representatives of the class are identical. In reality, the process, the length and outcome of an infection is different for different individuals and this can have a substantial effect on the development of an epidemic. In the classical epidemic models, if there is no influx of new susceptibles (newborns or immigrants) and if infected individuals become immune after recovery (or die), the epidemic dies out.

The need for incorporating the immune system mechanism into epidemiological models has been recognized in several publications [3–5]. Here we propose a simple immunoepidemiological model incorporating a viral – immune response model with immune memory embedded in an epidemic network model. The network consists of individuals who can be infected and, depending on their 'immune status', can clear the virus and build an immune memory or have a persistent infection, characterized by the non-zero presence of virus, effector and memory cells. We demonstrate that even if each separate individual in a population is able to effectively clear the virus and build an immune memory when isolated from other infected individuals, the viral infection can persist in the network. No births or other introduction of new susceptibles is necessary for the infection to persist.

A model of viral spread in a population with a similar structure was proposed in [6]. Our model has a more realistic immune response component by including a mechanism of creating immunological memory. While in models without memory the immune system returns to its initial, 'virgin' state after the virus has been cleared, our immune response model results in the establishment of a pool of immune memory cells that remains after the clearance of the virus and is able to enact the secondary, higher-level immune response. Our study has a different goal and orientation from the one in [6], which is mainly interested in the spatial features of an epidemic and bases its conclusions on results from simulations. We are interested in the persistence of the virus in a population of hosts and prove that it can be maintained by the cohabitation of relatively immunologically weak individuals constantly exchanging virus who would otherwise recover completely (if living separately from each other).

2. The immunological model

Contemporary immunology reveals with astonishing detail the mechanisms of the immune system [7]. The immune response to a viral infection is a complex mechanism involving effector, helper and memory T cells and effector and memory B cells, proliferating from naive T and B cells, antibodies produced by the B cells, innate memory mechanisms, etc. This process has been modeled in various details and assumptions by many authors (for reviews, see [8,9]). It has been postulated that while B cells and their antibodies are an important part of the adaptive immune response mechanism, they are not able to clear a viral infection; the leading immune response is effected by the T cells [7]. We consider a simple viral dynamics model including the intracellular virus V and T cell (effector and memory) concentrations. We have conceived the model so that it has the simplest form that accounts for the formation of immune memory after infection. Our goal is to study the effect of individual responses on the outcome of an epidemic at the population level. The virus, T effector and T memory cells concentrations are denoted by V, T and M, respectively. The virus is assumed to have a constant replication rate r. It is cleared by effector T cells. We assume that the quantity of infected cells is proportional to the amount of virus and that the probability P_E of an effector cell to detect and destroy an infected cell is proportional to the quantity of infected cells. We deduce that $P_E = sV$ where s is a constant. Based on recent evidence [10] that memory cells participate actively in the immune response, the model assumes that memory cells also kill infected cells. Similarly to above, the probability of a memory cell to detect and destroy an infected cell is presumed to be equal to qV where q is a constant. Effector and memory T cells are produced from a constant common pool N^* of naive cells in the presence of virus with rates αV and βV, respectively. Effector T cells decay with a constant rate μ while memory cells maintain homeostasis effected by a logistic law mechanism. Thus, we obtain the model

$$\begin{aligned}\frac{dV}{dt} &= rV - sVT - qVM,\\ \frac{dT}{dt} &= \alpha VN^* - \mu T,\\ \frac{dM}{dt} &= \beta VN^* + (\gamma - \delta M)M.\end{aligned} \tag{2.1}$$

If the specific virus strain has never been presented to the immune system of the isolated host, the system (2.1) is accompanied by initial conditions $V(0) = T(0) = M(0) = 0$ and then has the unique $(0,0,0)$ solution for all times. In case that virus is present, the system has to be solved with some non-zero initial conditions for the virus concentration and its dynamics is easily described.

Namely, it can have two equilibria: $E_1 = (V_1^\infty, T_1^\infty, M_1^\infty) = (0,0,\frac{\gamma}{\delta})$ and, in case that $r - q\frac{\gamma}{\delta} > 0$, a positive equilibrium $E_2 = (V_2^\infty, T_2^\infty, M_2^\infty)$, where V_2^∞ is the unique positive solution of

$$r = \frac{\alpha s}{\mu} V_2^\infty N^* + \frac{q}{2}\left[\frac{\gamma}{\delta} + \sqrt{\left(\frac{\gamma}{\delta}\right)^2 + \frac{4\beta}{\delta} V_2^\infty N^*}\right] \tag{2.2}$$

and

$$M_2^\infty = \frac{\gamma}{2\delta} + \sqrt{\left(\frac{\gamma}{2\delta}\right)^2 + \frac{\beta}{\delta} V_2^\infty N^*}$$
$$T_2^\infty = \frac{\alpha N^*}{\mu} V_2^\infty. \tag{2.3}$$

I. If $\lambda_0 = r - q\frac{\gamma}{\delta} < 0$, E_2 does not exist and E_1 is globally asymptotically stable (Proposition 1 of the Appendix) which has the following meaning. The virus replication rate r and the per memory cell rate of virus elimination q are intrinsic to the virus and not variable among the individuals in the population, while $\frac{\gamma}{\delta}$, the homeostasis level of the virus-specific memory T cells, could vary from individual to individual. The virus-only-specific ratio $\frac{r}{q}$ represents the ratio of the number of viral particles produced by one virus per unit of time versus the number of viral particles destroyed by one memory cell per unit of time. We can call $\frac{r}{q}$ the in-host virus reproduction number. When this number is less than the memory cells homeostatic level M_1^∞, the virus gets cleared from the individual's organism and a pool of memory cells at the homeostatic level M_1^∞ is maintained, which represents the acquired immunity.

The model can reconstruct qualitatively observed viral and T-cell concentrations [11]. The T-cell concentration peaks when the virus has been removed (or is close to removal) and the memory cells gradually reach their homeostatic level. Fig. 1 shows plots of the viral, T cells and memory cells concentrations when solving the model with parameter values $r = 1$, $s = 0.2$, $q = 1.1$, $\alpha = 0.4$, $\mu = 0.03$, $\beta = 0.05$, $\gamma = 0.2$, $\delta = 0.2$, $N^* = 1$.

The model shows that an individual who was once presented with the virus and formed immune memory of it, clears the virus fast when presented with the virus later. Once the presentation of the virus terminates the in-host viral load decreases fast and the virus is cleared. Really, according to the model, such an individual would have a concentration of memory cells near the homeostatic level $\frac{\gamma}{\delta}$. Suppose that such an individual is presented with a new influx of virus $V_{\text{in}}(t)$ for a certain amount of time $t \in [0, T_0]$. We can write a model describing this individual's immune status as follows:

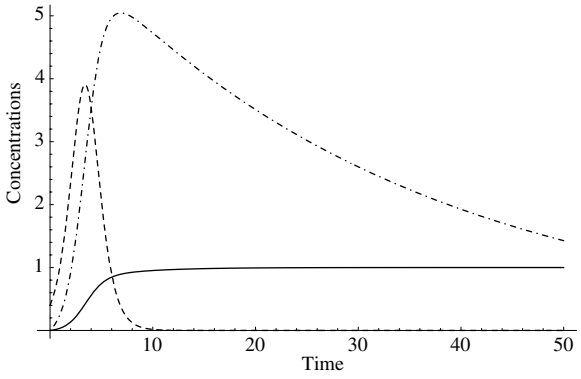

Fig. 1. A typical plot of viral load (dashed line), T-cell concentration (dot-dashed line) and memory T cells (solid line) concentrations generated by the immunological model. Time and concentrations units do not have physically meaningful values.

$$\begin{aligned}
&\frac{dV}{dt} = qV\left(\frac{r}{q} - M\right) - sVT + V_{in},\\
&\frac{dT}{dt} = \alpha VN^* - \mu T,\\
&\frac{dM}{dt} = \beta VN^* + (\gamma - \delta M)M,\\
&V(0) = V_{in}(0), T(0) = 0, M(0) = \frac{\gamma}{\delta},
\end{aligned} \tag{2.4}$$

where $V_{in} = 0$ for $t > T_0$. It is easy to see that $V(t) > 0$ and $M(t) > \frac{\gamma}{\delta}, \forall t$.

While an external virus influx persists (i.e. for $V_{in}(t) > 0$) the viral load $V(t)$ can increase but once the individual is no longer exposed to the virus, $V_{in}(t) = 0$ and $\left[\left(\frac{r}{q} - M\right) - \frac{s}{q}T\right]qV = \left[\left(\frac{\gamma}{\delta} - M\right)q - \frac{s}{q}T\right]V + \left(\frac{r}{q} - \frac{\gamma}{\delta}\right)qV$. Therefore, $V(t)$ decreases and in fact, because $\left(\frac{\gamma}{\delta} - M\right)q - \frac{s}{q}T < 0$, then $V(t) < V(t_0)e^{\left(\frac{r}{q} - \frac{\gamma}{\delta}\right)qt}$. So, the larger the difference between the in-host virus reproduction number and the memory cells homeostatic level, the higher the speed at which the virus is cleared. Therefore, different individuals who recover from infection will do so with different speeds.

II. If $\lambda_0 = r - q\frac{\gamma}{\delta} > 0$, E_1 is unstable as it has a positive eigenvalue λ_0. In this case, the positive equilibrium E_2 exists and is locally asymptotically stable (Proposition 2 of the Appendix). The interpretation of this result is that if the individual's homeostasis level of memory T cells is not sufficiently high, the virus does not get cleared and either persistent infection (with values of V, T, M approaching E_2 as t grows, or latent infection, with V, T, M oscillating around E_2) are possible. It is noteworthy to observe that $M_2^\infty > M_1^\infty$. That is, in the case of a persistent infection, the maintained quantity of the immune memory cells is higher than when the virus has been cleared and permanent immunity has been established. Because we are not proving global stability of E_2, persistent infection might not be the only outcome; there might be periodic or chaotic oscillations, characteristic of latent, reactivating infections. Independently of the outcome, in this case, in the presence of infection (i.e. $V(0) > 0$), $M(t)$ grows until it reaches a value larger than $\frac{\gamma}{\delta}$ and stays above this value. So, a state with non-clearing infection is characterized (according to the model) with high levels of immune memory cells (higher than the value established after a successfully cleared infection) and effector cells.

3. The immunoepidemiological model

We shall not explore any further the immunological model but will be interested in the following question. Suppose that all individuals in a population are able, when isolated from each other, to fully recover from a viral infection and build an immune memory response. Consider a population of K individuals, belonging to a network in the following sense. An infected individual sheds virus infecting some of the other individuals in the population, with whom the individual is 'connected'. The virus received by a susceptible individual from the infected individual is proportional to the infected individual's viral load. The constants of proportionality g_{ij} representing the proportion of the virus shed by individual j and received by individual i include factors such as

distance, loss of virus viability, etc. These parameters are a measure of both the contact rate and the virus infectivity specific to the receiving individual and we call them *transmission rates*. The values of g_{ij} determine whether individuals i and j are connected (if $g_{ij} \neq 0$) or not ($g_{ji} = 0$). We do not define explicitly the form of g_{ij}, but, in general, larger values g_{ij} would be due to shorter distances between individuals, stronger virus dispersal (depending on the virus specificity as well as on the individual's characteristics), as well as to environmental conditions (cooler, more humid environments). As we assume that g_{ij} have constant values, the model is restricted to cases in which the individuals are connected for indefinite time. Populations of communal animal species, herds of livestock or groups of people living together in a limited space (military, children camps, refugee camps) can be assumed to satisfy such assumptions.

The immunoepidemiological model is written as

$$\begin{aligned}
\frac{dV_i}{dt} &= r_i V_i - s_i V_i T_i - q_i V_i M_i + \sum_{j=1, j\neq i}^{K} g_{ij} V_j, \\
\frac{dT_i}{dt} &= \alpha_i V_i N_i^* - \mu_i T_i, \\
\frac{dM_i}{dt} &= \beta_i V_i N_i^* + (\gamma_i - \delta_i M_i) M_i, \quad i = 1, \ldots, K.
\end{aligned} \tag{3.1}$$

The system (3.1) has an infection-free equilibrium $V_i^\infty = 0$, $T_i^\infty = 0$, $M_i^\infty = \gamma_i/\delta_i$, $i = 1, 2, \ldots, K$. It can also have other equilibria, but in this paper we are not interested in them. Note that the notations $V_1^\infty, T_1^\infty, M_1^\infty$ and $V_2^\infty, T_2^\infty, M_2^\infty$ were also used in the previous section. Although they have a different meaning here, to keep the exposition simple, we are avoiding the introduction of new notations.

We ask the following question. Suppose that all individuals in a population are 'in good health', i.e. have an appropriate immune response such that they can clear an infection when isolated from each other. In our immunological model this is expressed by $r_i - q_i \frac{\gamma_i}{\delta_i} < 0$, $i = 1, \ldots, K$. Is it true then that the virus will be cleared in a population consisting of such individuals? Considering a population means that we assume that some of the individuals are connected between each other in the above sense, i.e. groups of connected individuals exchange virus and each individual elicits an immune response.

We now translate this question in the terms of non-linear dynamics. We assume that some of the individuals were infected initially, i.e. $V_{l_j}(0) \neq 0$ for some l_j, $j \in [1, \ldots, K]$. The virus gets cleared on the population level if it gets eliminated in each individual, i.e.

$$V_i(t) \to 0, t \to \infty \text{ for all } i = 1, \ldots, K. \tag{3.2}$$

Thus, the question is whether and when this asymptotic behavior is observed.

The answer is easy to find for a system of two individuals exchanging virus. Obviously, if the individuals are not connected, i.e. $g_{ij} = 0$ $\forall i,j$ then (3.2) holds. The infection-free equilibrium $(0, 0, M_1^\infty, 0, 0, M_2^\infty)$ in this case is unstable if

$$\left(\frac{r_1}{q_1} - M_1^\infty\right)\left(\frac{r_2}{q_2} - M_2^\infty\right) - g_{12} g_{21} < 0, \tag{3.3}$$

(and stable if the inequality is reversed, see Proposition 3 of the Appendix).

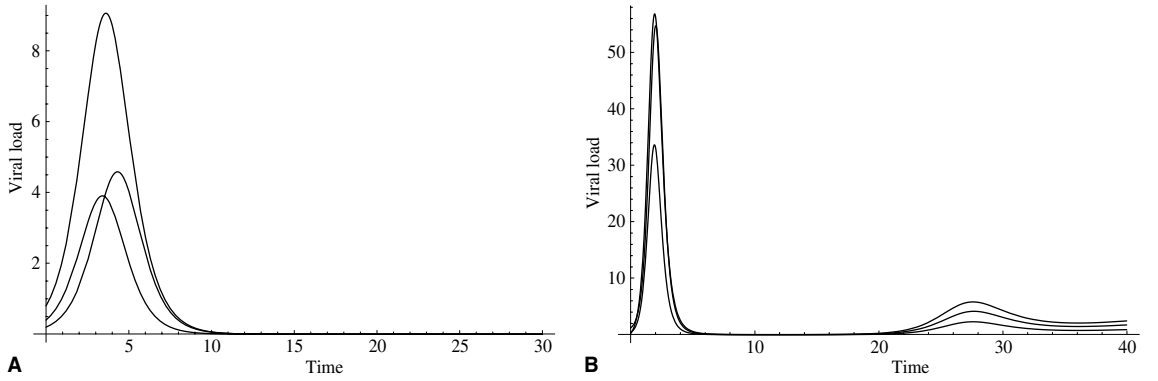

Fig. 2. Maintenance of persistent infection. Three individuals who, if living isolated from one another, would eliminate the virus, maintain persistent infection when living together. Note the synchronized bouts of secondary infection. Units do not have real meaning.

The quantities $\left(\frac{r_i}{q_i} - M_i^{\infty}\right)$ are *stability measures* of the infection-free status of *i*th individual. If $\left(\frac{r}{q} - M_1^{\infty}\right)$ is negative but close to zero, a small perturbation to the system (2.1) can destabilize the infection-free equilibrium. For example, the homeostatic memory cells level M_1^{∞} can decrease due to stress.

Therefore, if the product of the transmission rates is larger than the product of the stability measures, the infection-free equilibrium of (3.1) is unstable (having a positive eigenvalue) and $V_i(t)$ diverge away from 0. This can happen if the immune status of some of the individuals is such that the individual is in a close to unstable state ($r_i - q_i M_i \approx 0$) or when the transmission rates have comparatively high values (for example this can happen when the distance between the individuals is sufficiently small).

Systems of $K > 2$ individuals, have an unstable infection-free equilibrium whenever there is at least one couple of connected individuals, say m and l, such that, $(r_l - q_l M_l^{\infty})(r_m - q_m M_m^{\infty}) - g_{lm} g_{ml} < 0$ holds (see Proposition 4 in the Appendix). Thus, a single couple of individuals in fragile health maintaining persistent infection by reinfecting each other, can be the source of infection spreading along the whole subnetwork they participate in.

Fig. 2(A) and (B) present plots from solving the model (3.1) with $N = 3$ individuals. In Fig. 2(A) the individuals are not connected and each clears the virus, while the virus peaks are at times specific for the individual. In Fig. 2(B) we show the viral loads of the same individuals which are connected and reinfect each other. The model parameters corresponding to the plots are shown in the Appendix. In this case, the viral loads stabilize at a non-zero value, they peak much higher than when the individuals are isolated from each other and also, a second (and in some cases, a notable third) peak is possible. The latter corresponds to infection rebouts often observed in clinical cases.

4. Discussion

The result in this paper bears some important implications. First, it shows that conclusions about the course of infection in an individual animal (human) are no longer valid when the

individuals are connected in a network. The length of an infection in connected infected individuals is different and can change from finite to indefinite, persistent or chronic infection. The viral load peak is much higher in the connected case. While the infection can have a single viral load peak in isolated individuals, it can show rebouts when individuals reinfect each other. This also shows that laboratory studies of infection in individual animals may not be informative about the spread of infection in the wild.

Chronic infections reappearing in large groups of people living in a contained environment, like soldiers in a military base or children in a summer camp can be explained by the occurrence of persistent infections in individuals who would otherwise be able to recover. For example, adenoviruses are known to often cause infection among military recruits [12,13], and other young people who live in institutional environments and outbreaks among children are frequently reported at boarding schools and summer camps. The usual countermeasures consist of increasing hygiene, hospitalization and quarantine. The conclusions from our model show that a simple countermeasure could be to decrease the time the same groups of people spend together.

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Appendix

Proposition 1. *The equilibrium E_1 of (2.1) is globally asymptotically stable if $r - qM\frac{\gamma}{\delta} < 0$.*

Proof. Let $V_0 > 0$, $T_0 > 0$, $M_0 > 0$ be an initial condition of (2.1). It is easily established that $V(t) > 0$, $T(t) > 0$, $M(t) > 0$, $\forall t$. Note that the equations for V' and M' can be rewritten as

$$\begin{aligned} V' &= (r - qM_1^\infty)V - sVT - qV(M - M_1^\infty) \\ M' &= \beta VN^* - \delta M(M - M_1^\infty). \end{aligned} \tag{A.1}$$

One can solve the second equation implicitly

$$M(t) - M_1^\infty = (M_0 - M_1^\infty)\mathrm{e}^{-\int_0^t \delta M(\sigma)\mathrm{d}\sigma} + \int_0^t \beta N^* V(\tau)\mathrm{e}^{-\int_\tau^t \delta M(\sigma)\mathrm{d}\sigma}\mathrm{d}\tau. \tag{A.2}$$

(A) Therefore, if $M_0 - M_1^\infty > 0$, then $M(t) - M_1^\infty > 0, \forall t$ and from the first equation we see that in this case, $V(t)$ decreases monotonically and $V(t) \to 0$, $t \to \infty$.

(B) If $M_0 - M_1^\infty < 0, M(t)$ increases initially. There are two cases: (a) $M(t_*) = M_1^\infty, M'(t_*) > 0$ for some t_*: in this case $M(t) > M_1^\infty$ for $t > t_*$ and as in (A), $V(t) \to 0$, $t \to \infty$; (b) $M(t) < M_1^\infty, \forall t$, then M increases and converges to some value $M_* \leqslant M_1^\infty$. It follows that $V(t)$ should converge to some value V_* and then T should converge to some value T_*, such that $V = V_*$, $M = M_*$, $T = T_*$

nullify the right-hand side of (A.1). As the only equilibria are E_1 and E_2 and as $M_2^\infty > M_1^\infty$, it follows that $M(t) \to M_1^\infty$. Then $V(t) \to 0$, $T(t) \to 0$, $t \to \infty$. □

Proposition 2. *If* $r - q\frac{\gamma}{\delta} > 0, E_2$ *exists and is locally asymptotically stable.*

Proof. The right-hand side of (2.2) is monotonously increasing function of V and if $V = 0$, it is equal to $q\frac{\gamma}{\delta}$. Thus, Eq. (2.2) has a unique positive solution V_2^∞. M_2^∞ and T_2^∞ are obtained from (2.3).

The characteristic polynomial $\chi(\lambda)$ of the linearization of (2.1) at E_2 is

$$\chi(\lambda) = \lambda(\mu+\lambda)(\gamma - 2\delta M_2^\infty - \lambda) - \beta N^* q V_2^\infty(\mu+\lambda) + \alpha N^* s V_2^\infty(\gamma - 2\delta M_2^\infty - \lambda).$$

It can be written as

$$\chi(\lambda) = P_3(\lambda) + P_1(\lambda),$$

where $P_3(\lambda)$ is a third order polynomial with roots 0, $-\mu$ and $\gamma - 2\delta M_2^\infty = -\sqrt{\gamma^2 + 4\beta\delta V_2^\infty N^*} < 0$ and P_1 is a linear polynomial with a root

$$(-\mu)\cdot\frac{A}{A+B} + (\gamma - 2\delta M_2^\infty)\cdot\frac{B}{A+B},$$

where $A = \beta q > 0$ and $B = \alpha s > 0$.

P_1 has a negative slope and its root is located between the negative roots of P_3 as $A > 0$ and $B > 0$. These arguments show that $\chi(\lambda)$ has no non-negative roots and that it has as least one real negative root and that the smallest negative root λ_3 of $\chi(\lambda)$ is located between $-\mu$ and $\gamma - 2\delta M_2^\infty$.

Suppose that the roots of $\chi(\lambda)$ are $\lambda_3 < 0$ and a pair of complex roots $\lambda_{1,2} = x \pm \mathrm{i}y$. Then, $\lambda_1 + \lambda_2 + \lambda_3 = \lambda_3 + 2x = -\mu + \gamma - 2\delta M_2^\infty < 0$, i.e. $2x = -\mu + \gamma - 2\delta M_2^\infty - \lambda_3$. Since both $-\mu$ and $\gamma - 2\delta M_2^\infty$ are negative quantities, and at least one of them is less than λ_3, it follows that $x < 0$.

Therefore, if it exists, E_2 is locally asymptotically stable. □

Proposition 3. *If* $K = 2$ *and* $r_i - q_i\frac{\gamma_i}{\delta_i} < 0$, $i = 1,2$, *the infection-free state* $(0,0,M_1^\infty,0,0,M_2^\infty)$ *of* (3.1) *is unstable if*

$$\left(r_1 - q_1\frac{\gamma_2}{\delta_1}\right)\left(r_2 - q_2\frac{\gamma_2}{\delta_2}\right) - g_{12}g_{21} < 0. \tag{A.3}$$

The equilibrium is locally asymptotically stable if the opposite inequality holds.

Proof. The Jacobian of (3.1) around the infection-free equilibrium is

$$\begin{vmatrix} r_1 - q_1\frac{\gamma_1}{\delta_1} & 0 & 0 & g_{12} & 0 & 0 \\ \alpha_1 N_1^* & -\mu_1 & 0 & 0 & 0 & 0 \\ \beta_1 N_1^* & 0 & -\gamma_1 & 0 & 0 & 0 \\ g_{21} & 0 & 0 & r_2 - q_2\frac{\gamma_2}{\delta_2} & 0 & 0 \\ 0 & 0 & 0 & \alpha_2 N_2^* & -\mu_2 & 0 \\ 0 & 0 & 0 & \beta_2 N_2^* & 0 & -\gamma_2 \end{vmatrix}. \tag{A.4}$$

The characteristic equation then has the roots $-\mu_1, -\mu_2, -\gamma_1, -\gamma_2$ and the other two roots satisfy the equation

$$\begin{vmatrix} r_1 - q_1\frac{\gamma_1}{\delta_1} - \lambda & g_{12} \\ g_{21} & r_2 - q_2\frac{\gamma_2}{\delta_2} - \lambda \end{vmatrix} = 0. \tag{A.5}$$

If (A.3) is satisfied, the last equation has a positive root and the infection-free equilibrium is unstable. If the opposite inequality holds, both roots have a negative real part and the equilibrium is asymptotically stable. □

Proposition 4. *Systems of K individuals, $K > 2$ have unstable infection-free equilibrium whenever there is a couple of connected individuals, say, l and m, such that*

$$\left(r_l - q_l\frac{\gamma_l}{\delta_l}\right)\left(r_m - q_m\frac{\gamma_m}{\delta_m}\right) - g_{lm}g_{ml} < 0 \tag{A.6}$$

holds.

Proof. The stability of the equilibrium is determined by the value of the largest eigenvalue of the matrix

$$J = \begin{vmatrix} r_1 - q_1M_1^\infty & g_{12} & g_{13} & \cdots & g_{1K} \\ g_{21} & r_2 - q_2M_2^\infty & g_{23} & \cdots & g_{2k} \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ g_{k1} & g_{k2} & g_{k3} & \cdots & r_K - q_KM_K^\infty \end{vmatrix}, \tag{A.7}$$

where $M_i^\infty = \frac{\gamma_i}{\delta_i}$.

J is a matrix with non-negative off-diagonal elements. Such matrices are known as ML-matrices [14]. Any ML-matrix $\mathscr{M}$ has a real eigenvalue $\rho(\mathscr{M})$ which is larger or equal to the real part of any other eigenvalue [14]. Thus, J has a real eigenvalue $\rho(J)$ such that $\Re\lambda_i(J) \leqslant \rho(J)$ for all eigenvalues $\lambda_i(J)$ of J.

Next, we use a corollary of a majorization theorem (Theorem 1 in [15]). The theorem states that if $A = (a_{ij})$ and $B = (b_{ij})$ are two complex matrices such that $a_{ij} \geqslant |b_{ij}|$, $i \neq j$ and $a_{ii} \geqslant \Re b_{ii}$, then (because A is an ML-matrix) $\rho(A) \geqslant \max_i \Re\lambda_i(B)$, where $\lambda_i(B)$ are eigenvalues of B. The corollary then states that if $P = (p_{ij})$ and $Q = (q_{ij})$ are two ML-matrices with $p_{ij} \geqslant q_{ij}$, then $\rho(P) \geqslant \rho(Q)$.

Returning to the matrix J, let J_{ml} be a matrix obtained from J by replacing all g_{ik}, $i \neq k$, $i \neq l,m$, $k \neq l,m$ with zeros. Then $\rho(J_{ml}) \leqslant \rho(J)$. The spectrum of J_{ml} consists of the values $r_i - q_iM_i^\infty$, where $i \neq m,l$ and of the two eigenvalues of the matrix

$$J_{ml}^{(2)} = \begin{vmatrix} r_l - q_l\frac{\gamma_l}{\delta_l} & g_{lm} \\ g_{ml} & r_m - q_m\frac{\gamma_m}{\delta_m} - \lambda \end{vmatrix} = 0. \tag{A.8}$$

Since because of (A.6) $J_{ml}^{(2)}$ has a positive eigenvalue, it follows that $\rho(J) \geqslant \rho(J_{ml}) > 0$. □

Parameters for the model simulations presented in Fig. 2.

$$
\begin{aligned}
&r_1 = 1,\ s_1 = 0.2,\ q_1 = 1.1,\ \alpha_1 = 0.4,\ \mu_1 = 0.03,\ \beta_1 = 0.05,\ \gamma_1 = 0.2,\ \delta_1 = 0.2,\\
&N_1^* = 1,\ V_1(0) = 0.4,\ T_1(0) = M_1(0) = 0;\\
&r_2 = 1,\ s_2 = 0.1,\ q_2 = 0.65,\ \alpha_2 = 0.3,\ \mu_2 = 0.1,\ \beta_2 = 0.08,\ \gamma_2 = 0.5,\ \delta_2 = 0.2,\\
&N_2^* = 1,\ V_2(0) = 0.2,\ T_2(0) = M_2(0) = 0;\\
&r_3 = 1,\ s_3 = 0.1,\ q_3 = 0.7,\ \alpha_3 = 0.5,\ \mu_3 = 0.2,\ \beta_3 = 0.02,\ \gamma_3 = 0.3,\ \delta_3 = 0.1,\\
&N_3^* = 1,\ V_3(0) = 1.2,\ T_3(0) = M_3(0) = 0;\\
&g_{12} = 0.6,\ g_{21} = 0.7,\ g_{13} = 0.7,\ g_{23} = 2,\ g_{31} = 0.8,\ g_{32} = 0.9.
\end{aligned}
\tag{A.9}
$$

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